5,763,178) and Chee et al. (U.S. Patent 5,837,832). This rejection, to the extent that it applies to the claims as amended, is respectfully traversed.

The requirements of a *prima facie* case of obviousness are set forth in MPEP 2143:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Applicants maintain their previous arguments regarding the cited publications and their relationship to the claimed invention. In response to the Applicants' arguments, the Examiner asserts that Applicant has acknowledged that "Chee et al. teach that probes may be 'very long' and in particular they teach the claimed probes having **part of** a sequence of full-length gene" as recited in the instant claims.

Gifford et al discloses a system comprising a full-length cDNA as reference oligonucleotide on a solid support, and a test oligonucleotide. Mut-S and other proteins bind to mismatched bases. Then, the presence of mismatched bases is carried out by electrophoresis or by isolation using Mut-S bound to a matrix (purification). Unlike the technique of thee presently claimed invention, the Gifford et al. technique permits the user to examine only one sequence at a time. A user wishes to analyze more than one sequence must perform a separate electrophoresis step for each sequence to be examined.

With regard to Chee et al., no statement has been made by Applicant acknowledging that Chee et al. teach that probes may be "very long." Quite the contrary. Applicant's previous response points out that Chee et al. teach only *short* probes. The Examiner cites column 7, lines 2-5 and 55-57 in support of the term "very long probes". However, a careful review of Chee reveals that Column 7, lines 58-61 says that "probes for long stretches of DNA coding regions to be directly "written" onto the chips in the form of sets of overlapping oligonucleotides". This means that the nucleotide sequence of a coding region of a gene is divided in probes (short oligos) overlapping each other. At most, Chee et al. teach a mixture of contiguous short probes that represent a long sequence (*e.g.*, "tiling method" (column 8, lines 17-29) which requires that a high number (~1296) of very short probes (preferably 10-18 bases) overlaps in order to cover the full length of an exon). However, Chee in no way

teaches long probes. Applicants respectfully submit that the term "very long sequence" can only be understood as a probe which is short when compared to a full-length sequence.

In fact, the method used by Chee is the VLSIPS method (*see* column 5, lines 53-55). Using VLSIPS, one can *synthesize* arrays of many thousands of oligonucleotide probes on a substrate, such as a glass slide or chip. The VLSIPS method (see also http://www.affymetrix.com/about/press/Old/pr930415.html) is therefore a method for synthesizing (that is creating) oligos (probes) *on the substrate.* Chee et al. do not attach or fix existing sequences on a substrate. It was well known in the art, at the time the present invention was made, that an oligo synthesized on a substrate or support has to be short. Current methodologies do not allow the synthesis of very long probes on a substrate. This is confirmed by the fact that the claims of the Chee patent (*see, e.g.,* claim 1) are limited to probes of 9 to 20 nucleotides.

With regard to the Examiner's argument that the recitation of "part of" the sequence of a full-length gene covers the short probes taught by Chee, Applicants disagree. When read in the context of the present claims, the recitation of "part of" a full-length sequence would be understood by one of ordinary skill in the art to mean sequences too long to be encompassed by the short probes of Chee et al. Nevertheless, without conceding to the Examiner's arguments, but solely in an effort to expedite prosecution, claims 1, 9, and 28 have been amended to delete reference to "part of" the sequence of a full length gene. As none of the cited publications either disclose or suggest the use of a full-length sequence, as required by the amended claims, these claims cannot render the presently claimed invention *prima facie* obvious. Withdrawal of this rejection is thus respectfully requested.

Claims 9-18 are rejected under 35 U.S.C.§103(a) as purportedly obvious over Chirikjian et al., in view of Chee et al., and further in view of Goldrick et al. (U.S. Patent 5,891,629). This rejection, to the extent that it applies to the claims as amended, is respectfully traversed.

The deficiencies of Chirikjian et al. and Chee et al. are discussed above. The Examiner concedes that Chirikjian et al. does not disclose S1 nuclease, Mung bean nuclease, or RNase H, but argues that Goldrick et al. "teaches a method for detecting point mutations in nucleic acids using nuclease, *i.e.,* S1 nuclease, Mung bean nuclease and any

or all of the RNases." However, Goldrick et al. does not cure the principal deficiencies of the combination of Chirikjian et al. and Chee et al. These two patents, taken together (or alone) neither disclose nor suggest the use of all of a full-length sequence as a probe, as required by the present claims. Accordingly, claims 9-18 are not *prima facie* obvious over Chirikjian et al., neither in view of Chee et al., nor further in view of Goldrick et al. Withdrawal of this rejection is thus respectfully requested.

Claims 28-30 are rejected under 35 U.S.C.§103(a) as purportedly obvious over Chee et al. (U.S. Patent 5,837,832) in view of Chirikjian et al. (U.S. Patent 5,763,178). This rejection, to the extent that it applies to the claims as amended, is respectfully traversed.

The deficiencies of Chirikjian et al. and Chee et al. are discussed above. Neither patent discloses, or suggests, the use of all of a full-length sequence as a probe, as required by the present claims. Accordingly, claims 28-30 are not *prima facie* obvious over Chee et al. in view of Chirikjian et al. Withdrawal of this rejection is thus respectfully requested.

Claims 23-25 are rejected under 35 U.S.C.§103(a) as purportedly obvious over Gifford (U.S. Patent 5,750,335) in view of Zoltukhin et al. (U.S. patent 5,874,304) and Fleck et al. (*Nucl. Acids Res.* 22:5289-5295, 1994). This rejection, to the extent that it applies to the claims as amended, is respectfully traversed.

The deficiencies of Gifford are discussed above. The Gifford patent does not disclose, or suggest, the use of all of a full-length sequence as a probe, as required by the present claims. Neither the alleged teaching of GFP as a label by Zoltukhin et al., nor the alleged teaching of the Mut S homolog of *S. pombe*, remedies this deficiency. Accordingly, claims 23-25 are not *prima facie* obvious over Gifford in view of Zoltukhin et al. and Fleck et al. Withdrawal of this rejection is thus respectfully requested.

From the foregoing, further and favorable reconsideration in the form of a Notice of Allowance is believed to be next in order and such action is earnestly solicited.

In the event that there are any questions concerning this amendment, or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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